

## **REMARKS**

The Advisory Action of August 21, 2009 and the final Office Action of May 19, 2009 have been carefully studied. Favorable reconsideration and allowance of the claims are respectfully requested.

### **I. Claim Status and Amendments**

In the Advisory Action, the examiner indicates that the amendments and arguments in the Supplemental Amendment of August 18, 2009 will be entered for purposes of appeal but they are unpersuasive. The arguments in the after final Supplemental Amendment of August 18, 2009, which should be entered by way of the filing of the RCE, are reiterated herein by reference as they apply to the claims as amended herein.

Claims 25-28 and 35 presently appear in this application and stand rejected. No claims have been allowed.

By way of the present amendment, the claims have been amended to correct typographical errors. Also, Applicants have amended claims 25, 27, and 35 to delete the term "hydrate" appearing in the definition of Crystal Form E. This amendment is based on the description on page 7, lines 19-22. Claim 27 is amended to correct the term "patterns" to "pattern." No new matter has been added.

Further, claims 25-28 and 35 have been revised to specify the Crystal Form D as having a "residual solvent content of 1500 ppm or below." Applicants believe that this amendment is not new matter. Hiraide et al. (US patent application publication no. US2003/191296, corresponding to US application no. 10/399,126) (submitted with the response filed March 17, 2009) appears to disclose that the Crystal Form D prepared from Crystal Form E is the same as the Crystal Form D claimed in the present application. Hiraide et al., at paragraph [0010], clearly discloses that the content of the residual solvent is 1500

ppm or below. That being the case, it is inherent that the Crystal Form D claimed has a residual solvent content and particle size the same as the Crystal Form D disclosed in Hiraide. Since these are inherent properties of the Crystal Form D prepared by the claimed method, this amendment should not be considered new matter. See *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971), wherein the court cited with approval the holding in *Technicon Instruments Corp. v. Coleman Instruments, Inc.*, 255 F.Supp. 630, 640-41, 150 USPQ 227, 236 (N.D.Ill.1966), aff'd, 385 F.2d 391, 155 USPQ 369 (7th Cir.1967), that: By disclosing in a patent application a device that inherently performs a function, operates according to a theory, or has an advantage, a patent applicant necessarily discloses that function, theory, or advantage even though he says nothing concerning it, and it was concluded that the express description of the inherent property, since not "new matter", could be added to the specification with effect as of the original filing date. See also *Kennecott Corporation v Kyocera International, Inc. and Kyoto Ceramic Co., Ltd.*, 835 F. 2d 1419, 5 USPQ2d 1194 (Federal Circuit 1987), in which case, the claimed invention in the '299 application covered a ceramic product, which was the same as the product in the '954 application, and has the same structure, and the court held that the disclosure in a subsequent patent application of an inherent property of a product does not deprive that product of the benefit of an earlier filing date, nor does the inclusion of a description of that property in later-filed claims change this reasonable result. Following the logic in these cases, Applicants believe that the above amendment should not be new matter.

## **II. Prior Art Rejections**

Claims 28 and 35 remain rejected under 35 U.S.C. 102(b) as being anticipated by Miura et al. (US 5,959,088) for the reasons on pages 2-3 of the final Office Action.

Claims 8-11, 25-28 and 35 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Miura in view of Spanton et al. (US 5,945,405) for the reasons on pages 3-4 of the final Office Action.

Claims 16-18, 23, 25 and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Miura in view of Spanton and Bosch (US 6,504,017) for the reasons on pages 4-5 of the final Office Action.

These rejections are respectfully traversed and will be discussed together below, as Miura is the primary reference used in each rejection. The arguments in the after final Supplemental Amendment filed August 18, 2009 are reiterated herein by reference.

In the Advisory Action, the Examiner indicates that the amendments and arguments in the Supplemental Amendment of August 18, 2009 are unpersuasive. In particular, in item 11 of the Advisory Action, the examiner states that “Applicant contends that D-type crystal prepared via E-type crystal ensures a residual solvent content of 15000 ppm or below, which would not be achieved by the prior art D-type crystal.” The Examiner further states that “Applicant further argues that the claimed D-type crystals differ from the D-type crystals disclosed in Muir both in particle size and the amount of residual solvent.” The Examiner argues that such arguments are unpersuasive. In doing so, the examiner states that “[t]he present claims do not state the amount of residual solvent present” and he argues that the claimed compounds are identified by 2 or 3 peaks as measured by X-ray diffractometry, which is insufficient to identify a specific compound having a specific particle size. Applicants respectfully disagree.

First, it should first be noted the Examiner characterization of Applicants’ arguments is erroneous. Applicants, in the last response, argued that D-type crystal prepared

via E-type crystal ensures a residual solvent content of 1500 ppm or below, and not 15000 ppm or below.

Second, as to the anticipation rejection of claims 28 and 35 over Muira, Applicants respectfully submit that the claims need not state the amount of residual solvent present. In this regard, it should be noted that both claims 28 and 35 claim Crystal Form D of a hemifumarate hydrate of a compound of formula (I), which crystal is obtained from Crystal Form E. Accordingly, claims 28 and 35 are product-by-process type claims. Muira fails to disclose or suggest the process for making the product of the claims. This is significant given that the recited process imparts distinct properties and characteristics on the claimed product. Pursuant to US practice as discussed at MPEP § 2113, “[t]he structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.” See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979).

In the instant case, the process as recited in the claims for making the Crystal Form D of a hemifumarate hydrate imparts distinct structural characteristics and properties in the claimed final products for the reasons discussed in the last response. Again, the Crystal Form D prepared from Crystal Form E possesses superior properties, including reduced content of residual solvent and a larger particle size. It should be noted that Applicants previously presented evidence of these different properties by reference to Hiraide et al., U.S. Application No. 10/399,126, Published Application 2003/0191296, a copy of which was previously submitted. These properties are recited in the specification of Hiraide et al. It can be seen from Hiraide that the Crystal Form D prepared from Crystal Form E as claimed

herein is different from the Crystal Form D of Miura in content of residual solvent and particle size. In other words, Crystal Form D as claimed herein is a new substance.

Therefore, it is respectfully submitted that the Examiner's arguments that the compound in Molecular formula (I) as claimed in claims 28 and 35 is an old compound is groundless and improper.

As previously argued, in Hiraide, for instance, at paragraph 0010, it is noted that prior art D-type crystals prepared by conventionally known techniques have a number of problems, including a large volume of crystallization solvent remaining in the crystal as a residual solvent; the residual solvent is difficult to remove during drying, and the dryness of the residual solvent cannot be below 1500 ppm. The prior art D-type crystal also involves another problem of having a small particle size, which makes it difficult to prepare tablets comprising this crystal. Thus, it should be apparent that the prior art D-type crystal of Miura, prepared such conventionally known techniques, has the above-noted problems, which the claimed compounds do not. Again, the Crystal Form D claimed herein differs from the Crystal Form D of Miura in content of residual solvent and particle size, both of which differences would not be expected because the preparation of the two compounds is different.

It is well established patent law that in order to have anticipation, the prior art reference must disclose each and every element of a claim. In the present case, Miura mentions nothing with respect to the process for making the claimed product. Accordingly, there is nothing in Muira that discloses the particular Crystal Form D claimed herein, as the method of making the Crystal Form D claimed herein is different from that of Miura and provides unexpectedly superior properties of the claimed compound. In other words, Muira does not disclose or suggest the recited process for making the claimed product. As such and since the prior art product is made by a different method, the prior art product cannot have the

same distinct features resulting from the process recited in the claims. Thus, contrary to the position in the Advisory Action, it should not matter that the claims do not state the amount of residual solvent present, as the claims still recite the process and such properties inherently follow from the recited process.

For these reasons, the anticipation rejection over claims 28 and 35 over Miura is untenable and should be withdrawn.

Nonetheless, to expedite prosecution, Applicants have amended the claims to specify the residual solvent present resulting from the recited process. In particular, claims 25-28 and 35 have been amended to specify the Crystal Form D as having a "residual solvent content of 1500 ppm or below." Clearly, none of the cited prior art references disclose or suggest this feature of the claims.

It is believed that the above arguments and amendments also apply to and overcome the obviousness rejection over Miura and Spanton and the obviousness rejection over Miura, Spanton, and Bosch.

Again, Miura fails to disclose or suggest each and every element of claims, namely, the process claimed herein for making the product.

The secondary references of Spanton and Bosch fail to remedy the deficiencies in Miura. The claims in the present application are directed to the Crystal form D produced by the process claimed herein that differs from the Crystal form D disclosed in Miura both in particle size and in the amount of residual solvent. Therefore, the Crystal Form D produced by the process claimed herein is different from the prior art Crystal Form D.

Spanton adds nothing to Miura, as Spanton merely discloses tetrahydrofuran solvates of erythromycin derivatives. There is nothing in Spanton that suggests the Crystal

Forms claimed herein or the recited process for making them. The same is true for Bosch.

There is nothing in Bosch that suggests the Crystal Forms claimed herein or the recited process for making them.

Further, as set forth in MPEP § 2145, it is well established that obviousness can be rebutted by presenting rebuttal evidence, which may include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Applicants again point out to Hiraide (previously presented) as providing this type of rebuttal evidence.

As previously argued and as shown below, Table 1 of Hiraide discloses Crystal Form D prepared by Examples 2 to 8 and Comparison Examples 1 and 2.

TABLE 1

	Percentage of water (%)	Prepared via E-type crystal	Conditions for conversion of E-type crystal into D-type crystal	Drying conditions	Content of residual solvent (ppm)	Particle size ( $\mu$ m)	Tabletting troubles
Example 2	2.4	Completely	15° C., 3 hr $\rightarrow$ -10° C.	Reduced pressure 60° C., 8 hr	78	302	—
Example 3	2.6	Completely	15° C., 6 hr $\rightarrow$ -10° C.	Reduced pressure 60° C., 8 hr	—	197	—
Example 4	2.0	Partially	15° C., 1 hr $\rightarrow$ -10° C.	Reduced pressure 60° C., 28 hr	988	141	No
Example 5	2.0	Partially	15° C., 1 hr $\rightarrow$ -10° C.	Reduced pressure 60° C., 10 hr	845	197	No
Example 6	2.0	Partially	13° C., 0.5 hr $\rightarrow$ -10° C.	Reduced pressure 60° C., 9 hr	1049	—	—
Example 7	2.0	Partially	15° C., 1 hr $\rightarrow$ -10° C.	Reduced pressure 60° C., 6 hr	647	163	No
Example 8	2.0	Partially	15° C., 1 hr $\rightarrow$ -10° C.	Reduced pressure 60° C., 10 hr	893	185	No
Comparison Example 1	1.5	Not	—	Reduced pressure 60° C., 16 hr	2228	82	Yes
Comparison Example 2	1.5	Not	—	Aeration 45° C., 20 hr	1610	61	Yes

As shown in Table 1, Crystal Form E was not detected in a process of Comparison Examples 1 and 2 in which ethyl acetate containing 1.5% water was used. Miura used a mixture of 1.5 ml water and 100 ml ethyl acetate in Example 8, lines 4-6. Comparing the process of the above Comparison Examples with that disclosed in Miura, ethyl acetate containing 1.5%

water was commonly used in the processes recited in Table 1 and in Miura. Therefore, Crystal Form E was not formed in a process of preparing Crystal Form D disclosed in Miura, as well as in the process disclosed in Comparison Examples 1 and 2 of Table 1 above. Taking the foregoing into consideration, the process and Crystal Form D produced thereby disclosed in Comparison Examples 1 and 2 correspond to the process and Crystal Form D produced and thereby disclosed in Miura.

On the other hand, in the processes of Examples 2 and 8 of the above Table 1, Crystal Form E was detected in the process of preparing Crystal Form D. Crystal Form D was also prepared via Crystal Form E in the presently claimed process. Taking the foregoing into consideration, the processes and the Crystal Form D produced thereby disclosed in Examples 1-8 correspond to the process claimed herein and Crystal Form D produced thereby.

According to Hiraide, Crystal Form D obtained via Crystal Form E has a residual solvent content of 78, 988, 845, 1049, 647 or 893 ppm and a particle size of 302, 197, 141, 197, 163 or 185 microns. On the other hand, Crystal Form D obtained without forming Crystal Form E has a residual solvent content of 2228 or 1610 ppm and a particle size of 82 or 61 microns. It can thus readily be seen that the Crystal Form D claimed herein is different from the Crystal Form D disclosed in Miura in both the amount of residual solvent content and the particle size. It is respectfully submitted that such results are evidence of the superior properties of the claimed invention.

In light of the above, it is respectfully submitted that Crystal Form D, which is obtained from Crystal Form E by the process recited in the present claims, is novel and nonobviousness over Crystal Form D that is not obtained via Crystal Form E and disclosed in Miura.



These properties are neither disclosed nor suggested in Miura, Spanton or Bosch. There is nothing in any of the cited references, alone or in combination, that would lead one skilled in the art to predict the properties of Crystal Form D obtained by preparing Crystal Form D from Crystal form E.

Therefore, it is respectfully submitted that the processes recited in claims 25-27 are not obvious over Miura in view of Spanton and/or Bosch, and it is respectfully requested that the rejection of these claims be withdrawn. In addition, Crystal Form D recited in claims 26, 28 and 35 is not obvious over Miura in view of Spanton and Bosch for the same reasons.

**III. Conclusion**

Favorable consideration and allowance are requested in view of the above.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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